hypertension. Tablets are prepared from these compositions preferably using a wet granulation process. (Column 6, Lines 27-31). This reference is devoid of any mention of valsartan.

The Examiner is of the belief that Applicants' invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made. According to the Examiner, since Fujimura teaches that valsartan is an angiotensin type II receptor antagonist and Ku teaches that irbesartan is a potent angiotensin type II receptor antagonist, one having ordinary skill in the art would have a reasonable expectation that the method described by Ku for pharmaceutical compositions containing irbesartan would be successfully applicable to create pharmaceutical compositions containing valsartan suitable to prepare compressed solid dosage forms. The Applicants respectfully disagree.

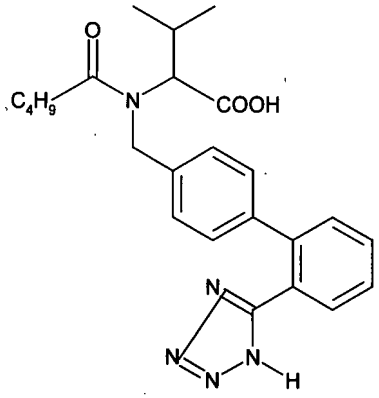
> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure.
>
> Section 706.02(j) M.P.E.P. (citing *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)).

Applicants respectfully disagree with the Examiner's statement that "it would have been obvious to one of ordinary skill in the art at the time the invention was made to synthesize a *compressed solid dosage form of valsartan or valsartan and hydrochlorothiazide , as disclosed by Fujimura et al....*" (Office Action at Page 4, emphasis added). Applicants respectfully submit that Fujimura does not disclose a "compressed solid dosage form" of valsartan since there is no information in this reference regarding the particular dosage form used in this study. The Examiner acknowledges that "Fujimura et al. does not provide the process for the preparation of the dosage forms of valsartan." (Office Action at Page 3).

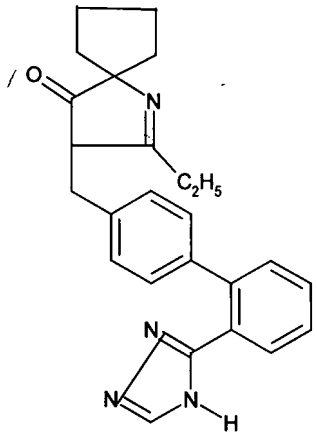
Applicants also respectfully disagree with the Examiner's belief that since valsartan and irbesartan are both angiotensin type II receptor antagonists, "one having ordinary skill in the art would have a reasonable expectation that the method described by Ku et al. for the pharmaceutical

compositions containing irbesartan would be successfully applicable to pharmaceutical compositions containing valsartan." (Office Action at Pages 4-5). Ku discloses suitable pharmaceutical compositions for the creation of tablets of irbesartan. This reference is devoid of any mention of valsartan; it does not motivate, teach or suggest that said compositions will be suitable to create small tablets of valsartan with a reasonable expectation of success. One of ordinary skill in the art recognizes that, while there may be some similarity in the chemical structure of these two compounds, there are also very real differences which can impact not only the nature and amount of excipients with which the active compound must be combined in order to create compositions suitable for tableting, but also the suitability of various tableting methods.

The chemical structures of valsartan and irbesartan are provided below:



Valsartan



Irbesartan

One of skill in the art will recognize that while these two compounds share a similar biphenyl-tetrazole ring structure, they have different side chains or functional groups; irbesartan is characterized by a double ring system while valsartan has a ring-free carboxy-ketone constituent. This difference in functional groups causes these compounds to have different physical and chemical properties. For example, the presence of the carboxylic acid in valsartan makes this compound more polar than irbesartan. This difference in polarity causes valsartan to be more soluble than irbesartan. Specifically, valsartan is soluble in ethanol, methanol and slightly soluble in water while irbesartan is only slightly soluble in alcohol and methylene chloride and is practically insoluble in water (See, for example, http://wwwrxlist.com). Thus, given these differences in solubility, Applicants respectfully submit that a formulation chemist would not have a reasonable expectation that the method described by Ku for pharmaceutical compositions containing irbesartan would be successfully applicable to create pharmaceutical compositions containing valsartan suitable to prepare compressed solid dosage forms.

In addition, it is interesting to note that the structural differences in side chains also contribute to very real differences in the pharmacological and pharmacokinetic properties of valsartan and irbesartan. This is true for the class as a whole; for example, while angiotensin type II receptor antagonists may share a common mechanism of action, they display differences in: binding kinetics to the AT1 receptor, oral bioavailability, half-life, food interaction, duration of action, protein binding, rate of absorption, metabolism, and rate and route of elimination, all of which may effect the efficacy or tolerability profiles of these compounds. (See, for example, Brunner, H. American Journal of Hypertension 10: 311S-317S (1997); Zusman, R. American Journal of Hypertension 12:231S-235S (1999)). While in the eyes of the formulation chemist, the pharmacological and pharmacokinetic properties of a drug may not be as important as the physical chemical properties, nevertheless, one of skill in the art would still take note of such differences and would be aware that one angiotensin type II receptor antagonist is not necessarily effectively interchangeable with another.

The unique chemical properties of angiotensin type II receptor antagonists have made it difficult in some cases to develop formulations useful for the creation of tablets. In the pending case, Applicants have focused on the particular physical properties of valsartan:

> [V]alsartan is difficult to formulate and heretofore it has not been possible to make oral formulations in the form of tablets in a reliable and robust way. Capsules are undesirable since large capsules must be used to accommodate effective amounts of active agent, which in the case of valsartan, is of low density and is therefore rather bulky.

(Specification at Page 1, Lines 18-23). The instant application includes claims directed to various compressed solid dosage forms of this compound as well as to a process to form such compressed solid dosage forms. In contrast, Ku addresses the specific problem of creating "pharmaceutical compositions of irbesartan, alone or in combination with a diuretic, which have good properties for tablet formation, and yet which contain a low mass of excipients so that small, easily swallowed tablets with a high content of active agent may be prepared." (Column 1, Lines 64-67, Column 2, Lines 1-2). According to Ku, such tablets are difficult to make because "[c]ertain physical properties of the drug present a challenge in developing formulations suitable for preparing a tablet having both a substantial quantity of active agent and a small enough tablet mass to allow ease of swallowing." (Column 1, Lines 44-47). Ku then mentions the specific properties of irbesartan which complicate the creation of small tablets of this compound- irbesartan is a fluffy material, with relatively low bulk and tap densities and it has undesirable flow characteristics, " for example is (sic) sticky and can adhere to surfaces such as tablet punch faces and dies, causing problems in tableting, especially on a high speed tablet press." (Column 1, Lines 52-56). Also problematic is the

"low aqueous solubility" of irbesartan, "since, to keep the tablet mass small, only limited amounts of excipients may be added to facilitate wetting, disintegration, and ultimately, rapid and complete drug release. The addition of a diuretic such as hydrochlorothiazide, which is also a fluffy material exhibiting poor flow and low aqueous solubility, can further contribute to tableting problems." (Column 1, Lines 56-63).

Applicants acknowledge that both valsartan and irbesartan are "fluffy"/"bulky" compounds with low bulk and tap densities, a characteristic that is typically encountered by formulators. However, despite this particular similarity, Applicants respectfully submit that the functional groups of these compounds are unique and thus effect the physical chemical properties of these compounds in ways (i.e. solubility, membrane permeability) which can have an impact on the formulation chemistry necessary for successful tablet creation.

In Applicants' response to the Office Action dated February 2, 2000, Applicants briefly alluded to the differences in the physical chemical properties of irbesartan and valsartan, specifically, that irbesartan is a sticky substance and valsartan has not shown this tendency, and because of this difference it is not *necessarily* true that the method disclosed by Ku to make tablets of irbesartan would also be applicable to make tablets of valsartan. The Examiner may be referring to this discussion in the pending Office Action by pointing out that Ku adds an antiadherent "because of the physical properties of the compound, but is not crucial for the purpose of preparing the tablets of the invention". (Office Action at Page 4). Applicants respectfully disagree with the Examiner's statement. It is *because* of the particular physical properties of irbesartan that tablet formation is difficult. Applicants suggest that Ku adds an antiadherent specifically to get around the "stickiness" problem which causes irbesartan to "adhere to surfaces such as tablet punch faces and dies, causing problems in tableting, especially on a high speed tablet press" (Column 1, Lines 54-56). Thus, Applicants respectfully submit that as disclosed by Ku, antiadherent *is* crucial for the purpose of preparing irbesartan tablets. In addition, it is the use of Ku's specific processing technique (i.e. wet granulation) along with the use of specific components (i.e. binder) that overcome irbesartan's "undesirable flow characteristics".

Applicants wish to take this opportunity to point out that Applicants' pharmaceutical compositions of valsartan do contain glidant to facilitate the flow of the compound. However, glidant (i.e. "antiadherent") was not added to the compositions to address the particular "stickiness" problem described by Ku. In fact, whether or not valsartan exhibits any unusual sticking problems when placed into tableting machinery was not an issue to Applicants at the time of invention. Applicants' previous statement that valsartan is not a "sticky" compound is based on this fact.

Applicants do acknowledge that to the formulation chemist, almost all compounds may be considered as having "undesirable flow characteristics" and it is because of this common problem that excipients are employed by formulation chemists. The key is, of course, knowing which excipients to add given the physical and chemical properties of a particular compound.

Applicants respectfully submit that since Ku does not address the particular physical and chemical properties of valsartan, Ku does not teach the unique combination of excipients that would be required for a pharmaceutical composition of valsartan suitable for the creation of small tablets. Thus, at best, one skilled in the art would only find the instant invention obvious to try, which is not proper grounds for an obviousness rejection.

> The admonition that "obvious to try" is not the standard under §103 has been directed mainly at two kinds of error. In some cases, what would have been "obvious to try" would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful. (*In re O'Farrell*, 853 F.2d 894, 7 USPQ2d 1673 (Fed. Cir. 1988)).

Contrary to the Examiner's belief that since both belong to the same class of compound, what works for irbesartan would obviously work with valsartan, Applicants respectfully submit that because of the physical chemical differences between these compounds, one of skill in the art would not expect to make small tablets of valsartan with a reasonable expectation of success by simply substituting valsartan for irbesartan in the pharmaceutical compositions disclosed in Ku. For example, Ku's compositions contain surfactants and binders; Applicants' compositions do not require these excipients. Thus, Ku's teachings are insufficient to render Applicants' invention *prima facie* obvious since one would need to experiment to discern which combination of excipients would be necessary to make the valsartan compositions suitable for tableting as well as to discern the appropriate tableting method to employ.

Finally, the Examiner points out in her rejection that Ku indicates that tablets may be prepared from the compositions by "any suitable method" and refers to an example from the Ku reference. (Office Action at Page 3). Applicants respectfully point out that the process referred to by the Examiner is a wet granulation process, and, in fact, according to Ku, the irbesartan tablets are "preferably" prepared from the compositions by a "wet granulation process." (See Column 6, Lines 27-30). Applicants respectfully submit that despite Ku's assertion that "any suitable method for forming tablets" may be used to form the irbesartan tablets, there is nothing in this reference that motivates, teaches or suggests any other tableting method. Indeed, given the particular physical

chemical properties of irbesartan and the particular excipients that make up the disclosed compositions, it is unclear that anything other than the disclosed wet granulation technique would work with these formulations. There is nothing in Ku that teaches one of ordinary skill in the art how to modify the particular compositions to make small tablets of irbesartan for use with, for example, a dry compression method. Certainly there is nothing in Ku that motivates, teaches or suggests how to make tablets of valsartan using the dry compression method as disclosed by Applicants. In fact, Applicants respectfully submit that their use of dry compression to make tablets from a compound with low bulk and tap density is actually an unconventional approach; Ku, like others of skill in the art, uses wet granulation which is commonly used to make tablets of compounds that are "fluffy" or "bulky". For this reason, Applicants' invention should not be considered *prima facie* obvious, since proceeding contrary to accepted wisdom is "strong evidence of unobviousness" (*In re Hedges* 783 F.2d 1038, 228 USPQ 865 (Fed. Cir. 1986)).

Applicants respectfully submit that, for the reasons discussed above, Fujimura in view of Ku does not render the instant invention *prima facie* obvious and respectfully request that this rejection be withdrawn.

Applicants believe that the arguments presented above successfully overcome all the Examiner's grounds for rejection and that the claims are allowable.

A Notice of Allowance is respectfully requested.

If there are any fees due in connection with this communication, including any fees for a required extension of time, such an extension is requested and the Commissioner is authorized to charge the fees to Deposit Account No. 19-0134 in the name of Novartis Corporation.

Respectfully submitted,

Diane Tso

Novartis Corporation
Patent and Trademark Dept.
564 Morris Avenue
Summit, NJ 07901-1027
(908) 522-6807

Diane Tso
Attorney for Applicants
Reg. No. 46,012

Date: March 12, 2001